Novel Tools for Investigating Brain-derived GPCRs in Mental Health Research

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The official link for this solicitation is: http://grants.nih.gov/grants/guide/pa-files/PA-10-081.html

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Description:

Background

G-protein coupled receptor proteins (GPCRs) are membrane bound proteins that serve to modulate cellular activities. Many of the GPCRs have potential significance in healthy mental function and in mental disorders, including receptors for serotonin, glutamate, dopamine, opioids, GABA, orexins, somatostatin, muscarinic, cannabinoid, adrenergic, Neuropeptide Y, corticotropin releasing factor (CRF) and others. Drugs targeting GPCRs are currently used in the treatment of mental health disorders such as schizophrenia, anxiety and depression. Yet identification or synthesis of selective agonists and antagonists to these particular receptor subtypes has proved daunting. A major disadvantage in this regard is the lack of knowledge about the three dimensional (3-D) structure of these receptors. To date, only a few crystal structures of GPCRs has been identified (including rhodopsin, and more recently human ß2-adrenergic receptor, human A2A adenosine receptor, and the ß1-adrenergic receptor). Using current technologies, researchers have had a difficult time isolating the protein from the lipid membrane with which it is normally highly integrated, while still maintaining its structure and function. In addition, many GPCRs are distributed diffusely in the brain, making it difficult to extract large enough quantities of protein for further analysis.

Identification of the 3-D structures of these important receptor subtypes could lead to very selective

agonists/antagonists which could aid researchers in identifying specific functions of each receptor subtype and potentially lead to development of more selective pharmacologic treatments for mental disorders, with fewer side effects. In addition, other novel tools and approaches that do not require the 3-D structure to be known, but that would enable researchers to selectively screen for compounds with high selectivity to the receptor (and minimize side effects) would be of great value.

Objectives

The purpose of this funding opportunity is to encourage small businesses to develop technologies and approaches (i.e., novel ways to use new or existing technologies) that will enable researchers to better study the structure and/or function of brain localized GPCRs and/or potentially identify novel selective and specific agonists/antagonists to these receptor subtypes, with a focus on mental health function or dysfunction. Technologies and approaches aimed at either known receptor subtypes or orphan receptors would be of potential interest to NIMH. Examples include, but are not limited to:

- Examples of novel technologies and approaches needed to further elucidate the function of GPCRs and/or identify selective agonists/antagonists may include one or more of the following: computational models, high throughput molecular or cell-based assays, behavioral models, molecular imaging techniques, novel crystallization strategies, novel technologies and/or approaches to increase the yield of GPCR protein, etc.
- Examples of specific tool applications: define structural relationships of GPCRs with small molecules, identify orphan GPCRs with mental health relevance, cell signaling measures, receptor purification, crystallization and/or 3-D structure identification, etc.
- Examples of mental health disorders: schizophrenia, depression, bipolar disorder, attention deficit hyperactivity disorder, anxiety disorders, eating disorders, Tourette’s syndrome, obsessive compulsive disorder, autism spectrum disorders, HIV-associated neurocognitive disorders, etc.

These lists are not meant to be exclusive.